

DIAGNOSTIC TEST PROPERTIES OF A MODEL-BASED CLINICAL BIOMARKER FOR SEPSIS IN CRITICAL CARE PATIENTS

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Sepsis is a serious medical condition characterized by a systemic inflammatory response syndrome (SIRS) due to infection. The incidence of sepsis in intensive care in NZ is 11.8%, has a mortality rate of 37.5%, and costs NZ\$100M per year. Guidelines recommend early intervention within 6 hours. However, blood culture test confirmation may take up to 48 hours, by which time the disease may be advanced, and only 51% of sepsis cases have a positive culture. Thus, due to delayed and often inconclusive data, physicians often pre-emptively prescribe broad-based antibiotic therapy, increasing antibiotic resistance and costs. In contrast, failure to prescribe antibiotics early can lead to increased sepsis mortality. Hence, there is a significant need for a timely, accurate and non-invasive sepsis diagnostic test to support clinical treatment decisions.

Insulin sensitivity is decreases with worsening patient condition. A validated model-based glycemic control protocol can estimate insulin sensitivity hourly or more frequently in “clinical real time”. The primary research hypothesis is that model-based insulin sensitivity and physiological characteristics can be used to diagnose sepsis and assess its severity in real-time, thus providing the earliest possible detection.

A clinical biomarker for sepsis was calculated from real-time, model-based insulin sensitivity glycemic control data and physiological data, including: temperature, heart rate, respiratory rate, blood pressure, SIRS score, and their respective hourly rates of change from 36 patients with sepsis. Patients were identified as having sepsis based on a clinically validated sepsis score (ss) of 2 or higher (ss = 0-4 for increasing severity). Kernel density estimates are used development of joint probability density profiles for these data and for classification. The stratified bootstrap method and in-sample estimates were used to estimate bounds for prediction error of the classification model created. Area under the receiver operator characteristic (ROC) curve (AUC) was calculated to evaluate the discriminative ability of the test across a full range of cutoff values. From the ROC, the optimal probability cutoff value for classification was determined

The clinical biomarker for sepsis diagnosis at an optimal probability cutoff value of 0.319 has 94.4% sensitivity, 94.4% specificity for in-sample error. The ROC AUC is 0.989 for in-sample data. Thus, the clinical biomarker provides an effective real-time negative predictive diagnostic for sepsis with high accuracy. Negative prediction enables clinicians to negate pre-emptive antibiotic prescription. These statistical methods will be used to analyse the diagnostic properties of a refined clinical biomarker to be developed from the ongoing prospective clinical trial at Christchurch Hospital.